

08/602,272



UNITED STATES DEPARTMENT OF COMMERCE  
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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08/602,272 02/16/96 ELLIOTT

EXAMINER
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HM21/0929

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 LEXINGTON MA 02173-4799

ART UNIT	PAPER NUMBER
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#15

1642  
DATE MAILED:

09/29/98

This is a communication from the examiner in charge of your application.  
 COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7/9/98

☒ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

- ☒ Claim(s) 6, 8-10, 12-32, 34-50 is/are pending in the application.  
 Of the above, claim(s) 16-28, 38-50 is/are withdrawn from consideration.  
☐ Claim(s) \_\_\_\_\_ is/are allowed.  
☒ Claim(s) 6, 8-10, 12-15, 29-32, 34-37 is/are rejected.  
☐ Claim(s) \_\_\_\_\_ is/are objected to.  
☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.  
☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.  
☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.  
☐ The specification is objected to by the Examiner.  
☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).  
☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.  
☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_  
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

- ☐ Notice of Reference Cited, PTO-892  
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_  
☐ Interview Summary, PTO-413  
☐ Notice of Draftsperson's Patent Drawing Review, PTO-948  
☐ Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES-

1. Claims 11 and 33 have been canceled.

Claims 9, 10, 12-13, 31-32, 34-35 have been amended.

Claims 6, 8-10, 12-32 and 34-50 are pending.

Claims 16-28 and 38-50, drawn to non-elected inventions, remain withdrawn from examination

Claims 6, 8-10, 12-15, 29-32 and 34-37 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 14-15 and 36-37 are rejected under 35 U.S.C. 112, first paragraph, as containing new matter in the recitation "competitively inhibits binding of TNF $\alpha$  to monoclonal antibody cA2," is withdrawn.

4. The rejection of claims 9-10, 12-13, 31-32 and 34-35 under 35 U.S.C. 112, second paragraph, is withdrawn. The rejection of claims 14-15 and 36-37 under 35 U.S.C. 112, second paragraph, is maintained.

The rejection of the claims based on the recitation "chimeric" in claims 9, 12-15, 31 and 34-37 is withdrawn in view of the amendments to the claims.

The rejection of the claims based on the recitation "binds to one or more epitopes" in claims 10, 13, 32 and 35 is withdrawn in view of the amendments to the claims, deleting this recitation.

The rejection of claims 14-15 and 36-37 based on the recitation "cA2" is maintained. It remains unclear whether "cA2" represents a genus of chimeric antibodies or a species, a unique chimeric clone. The applicant's arguments and the referenced portions of the specification do not clarify this issue.

5. The rejection of claims 14-15 and 36-37 under 35 U.S.C. § 112, first paragraph, as

failing to provide complete evidence of the deposit of the biological materials is withdrawn in view of incorporation by reference of the nucleic acid and amino acid sequences of both the light chain variable region and the heavy chain variable region of the cA2 antibody from issued U.S. Patents 5,698,195 and 5,656,272. It is noted that the applicants arguments based on In re Wands are not found persuasive. The applicant argues that "the present situation is closely analogous to the facts in Wands." This is not correct. The rejection at issue in Wands was based on the level of enablement required to produce additional members of a genus, antibodies of a given isotype, that bind to a defined antigen with a designated affinity. In the instant case, the issue is the level of enablement need to reproduce a given species, one unique antibody clone.

6. The rejection of claims 6, 8-10, 12-15, 29-32 and 43-37 under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure commensurate with the scope of the claims, is maintained.

The rejection of claims 6 and 29, broadly drawn to a method of treatment comprising the administration of a tumor necrosis factor "antagonist" is maintained. The applicant argues that it would not require undue experimentation to make and use "TNF antagonists" "since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen, it is expected, based on scientific reasoning, that the claimed invention works in the same manner using other antagonists." The application also argues that the specification discloses TNF antagonists to include anti-TNF antibodies, receptor molecules, agents which prevent or inhibit TNF synthesis or release, and agents which prevent or inhibit TNF receptor signaling. This has been carefully considered and is not found persuasive. By the applicant's own admission, they contemplate a "TNF antagonist" to encompass many classes of molecules (antibodies to receptors to agents that inhibit) that function to inhibit TNF activity via many different routes (antibody binding to cognate antigen; an agent inhibiting one of the multiple steps in receptor signaling; an agent inhibiting the synthesis of the TNF protein). Guidance for the making and using of this very broad collection of molecules can not be drawn from the making and using of antibodies in the

claimed method. Thus, one of skill in the art can not practice the claimed invention, without undue experimentation.

The rejection of claims 6, 8 and 29-30, drawn to treatment methods comprising the administration of antagonists and/or antibodies to tumor necrosis factor broad enough to read on the administration of murine antibodies, is withdrawn.

The rejection of claims 6, 8-10, 12-5, 29-32 and 34-37, broadly drawn to a method of treating or preventing thrombosis, is maintained. The rejection of claims 29-32 and 34-37, broadly drawn to a "method of decreasing plasma fibrinogen in an individual suffering from or at risk of thrombosis," is maintained.

The applicant argues the specification provides adequate teachings that thrombosis can be treated or prevented in an individual by administering a TNF antagonist, such as the cA2 chimeric antibody. This is not found persuasive. Active rheumatoid arthritis is a distinct disease state, with unique pathological parameters that are known to be associated with the increased production of TNF (see U.S. Patent 5,698,195 col.9, line 55-65). The specification teaches that the administration of anti-tumor necrosis antibodies to rheumatoid arthritis patients results in a decrease in elevated fibrinogen levels to a range closer to "normal," and "that the inhibition of the biological activity of tumor necrosis factor  $\alpha$  reduces fibrinogen and platelets levels in individuals with active rheumatoid arthritis" (see p. 2, lines 14-18). There is absolutely no evidence of record that outside of the context of the pathological state of rheumatoid arthritis, that anti-TNF antibodies influence fibrinogen levels and thrombosis. For example, the main presenting symptoms of rheumatoid arthritis are pain, stiffness, swelling and loss of function. Similar symptoms are also the main presenting symptoms in another form of arthritis, osteoarthritis. However, from studies of model systems for both rheumatoid and osteoarthritis, it is art accepted that anti-TNF antibodies would have a modulatory effect in only rheumatoid arthritis and not osteoarthritis (see U.S. Patent 5,698,195 (col 38, lines 46-55)). Thus, anti-TNF antibodies do not broadly inhibit joint pain and stiffness, from all causes. Likewise, one of skill in the art would not have a reasonable expectation of success, that anti-TNF antibodies would broadly "prevent thrombosis" or "decrease plasma fibrinogen," in any patient, regardless of the etiology.

✓ The rejection of the claims based the limitation binds "one or more epitopes" in claims 10, 13, 32 and 35 is withdrawn in view of amendments to the claims deleting said recitation.

7. The rejection of claims 29-30 under 35 U.S.C. 102(b) as being anticipated by van der Poll (Blood 83:446, 1994) is withdrawn.

8. The rejection of claims 31-32 and 34-7 under 35 U.S.C. 103(a) as being unpatentable over van der Poll (Blood 83:446, 1994) in view of WO 92/16553 is withdrawn.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

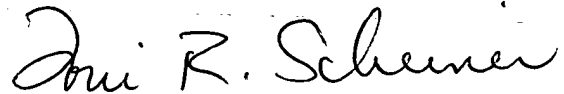
10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Johnson whose telephone number is (703) 305-5860. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [lila.feisee@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



TOM R. SCHEINER  
PRIMARY EXAMINER  
GROUP 1600



Nancy A. Johnson, Ph.D.

Patent Examiner, Group 1642

September 28, 1998